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Posttransfusion Purpura: Two Unusual Cases and a Literature Review

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INTRODUCTION

Posttransfusion purpura (PTP) is a rare but potentially lethal syndrome, characterized by the development of severe thrombocytopenia following transfusion [1–3]. Although the pathogenesis of this disorder remains poorly understood, patients with PTP present in a relatively characteristic manner which should be recognizable by the alert clinician. However, it is likely that many cases of PTP remain undiagnosed, and therefore the purpose of this report is to describe two cases of this disorder, and to provide a current review of its diagnosis, pathogenesis, and management.

CASE REPORTS

Case 1

G.H. was a 35-year-old African-American female with sickle-cell disease. Her past medical history was notable for recurrent painful crises with documented bony infarcts and lower-extremity ulceration. One month prior to admission to our institution, she was admitted to her community hospital with a painful crisis and temperature of 103°F. Therapy consisted of intravenous hydration, analgesia, and antibiotics, and led to a resolution of her symptoms over a 10-day period. Following discharge, however, her symptoms recurred, forcing readmission. A second course of therapy again led to resolution of her symptoms. However, she was admitted for a third time 3 days later, with recurrent pain and fever. Physical examination at this time revealed tachycardia, clear lung fields, and diffuse musculoskeletal tenderness. Hemoglobin was 7.6 g/dl, reticulocyte count 23.6%, platelet count 285,000, leukocyte count 9,800/μl, lactate dehydrogenase (LDH) 1,581, and total bilirubin 3.2. A chest X-ray revealed no active pulmonary disease. Due to gradually falling hemoglobin following admission, the patient received 4 units of packed red blood cells during the first week of her hospitalization. Approximately 7 days after the first transfusion, despite an improving clinical course, the patient developed recurrent fever, epistaxis, and gingival oozing, and a complete blood count (CBC) revealed a platelet count of 14,000/μl (Fig. 1A). She was transfused with 14 units of random donor platelets, and transferred for further care. Further questioning revealed that the patient had experienced one prior episode of thrombocytopenia approximately 5 years earlier, which had occurred following transfusions delivered in the setting of a ruptured ectopic pregnancy. She had also received multiple units of packed red cells in the past during management of painful crises, with several in the intervening interval since her ectopic pregnancy. Physical examination revealed crusted blood in the nares, a heme-positive stool, and both gingival and vaginal bleeding. Laboratory studies revealed a hemoglobin of 7.1 g/dl, leukocyte count of 23,000/μl, platelet count of 15,000/μl, LDH of 1,168, and total bilirubin of 10.1. Following bedside demonstration of a platelet-reactive antibody in the patient's serum (see Discussion), a provisional diagnosis of posttransfusion purpura (PTP) was made. The patient was treated with solumedrol, 60 mg intravenously every 12 h, and

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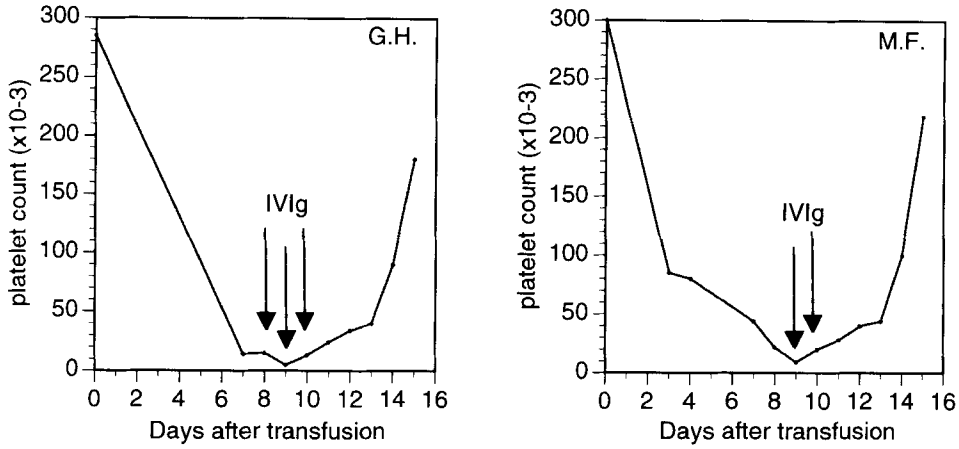

Fig. 1. Clinical courses of patients G.H. (A) and M.F. (B).

intravenous immunoglobulin, 1 g/kg the first day followed by 0.4 g/kg for the subsequent 2 days, with hormonal therapy instituted to control her vaginal bleeding. Although the platelet count fell to a nadir of 5,000/μl the day after transfer, it increased steadily thereafter, reaching 34,000/μl by day 5 of hospitalization, and increasing to normal by day 8. With the rising platelet count, the patient's hemorrhagic symptoms resolved.

Subsequent laboratory evaluation supported the initial diagnosis of posttransfusion purpura. Serologic typing of the patient's platelets revealed that she was a PL^{A1} homozygote whose episode of PTP was associated with the development of anti-PL^{A2} antibodies [4] (Fig. 2). In addition to anti-PL^{A2} antibodies, antibodies with specificity for 1) platelet glycoprotein (GB) IIb (later determined to be anti-Bak^a) and 2) an unidentified 85-kDa platelet protein (which comigrated with GP IIIa on nonreduced SDS-PAGE, but was separable from GP IIIa in 2D-PAGE, and was absent from PL^{A2}-negative platelets, but present on platelets from a donor with Glanzmann thrombasthenia), were detected in her acute-phase serum. It is possible that this second antibody recognized a proteolytic fragment of the cytoskeletal protein, vinculin [5], although the sera were reactive with intact platelets, as determined using a platelet-suspension immunofluorescence test (PSIFT) [6]. Based on these findings, we believe that this represents the second reported case of a patient with sickle-cell disease who developed PTP in association with both anti-PL^{A2} and anti-Bak^a antibodies [4,7].

Case 2

M.F. is a 44-year-old, gravida 4, Hispanic female who presented with a severe occipital headache, lethargy, and right-sided weakness (Fig. 1B). Admission laboratory studies revealed a hemoglobin of 11.5 g/dl, leukocyte count of 12,200/μl, and platelet count of 338,000/μl. Enhanced CT scan revealed a left middle cerebral artery aneurysm with surrounding hemorrhage. The patient was initially managed conservatively, receiving dilantin for seizure prophylaxis and multiple antibiotics for fever of uncertain etiology. Two weeks after admission she underwent surgical clipping of the left middle cerebral artery, receiving 2 units of packed red blood cells postoperatively. Four days later, a fall in platelet count to 80,000/μl was attributed to nafcillin-induced thrombocytopenia. After discontinuation of this medication, however, the platelet count continued to decline, reaching 26,000/μl by day 8 after transfusion (Fig. 1B). At this point the patient developed epistaxis, a heme-positive stool, and oozing from venipuncture sites. An infusion of 6 units of random donor platelets led to a severe febrile reaction, with no postinfusion platelet increment. After further infusion of 1 unit of single-donor platelets, and 2 units of leuko-filtered single donor platelets, the platelet count was 6,000/μl. At this point, the diagnosis of posttransfusion purpura was considered, and serologic testing revealed the presence of an antibody in the patient's serum which was reactive with all platelets against which it was tested, including those from a PL^{A1}-negative donor. These findings were consistent with the diagnosis of PTP, and, therefore, the patient was treated with intravenous immunoglobulin, 1 g/kg for 2 consecutive days. Her platelet count rose gradually thereafter, reaching 50,000/μl within 5 days of initial infusion, and achieving a normal value by day 15.

Additional studies were performed in attempts to immunologically characterize this patient's episode of PTP. Surprisingly, her serum contained anti-Br^a antibodies, as determined by radioimmunoprecipitation of a ~160-kD protein from detergent-solubilized platelets, making this patient approximately the third such individual in whom PTP has been attributed to antibodies of this specificity [1,8] (an additional case of *passive* thrombocytopenia,

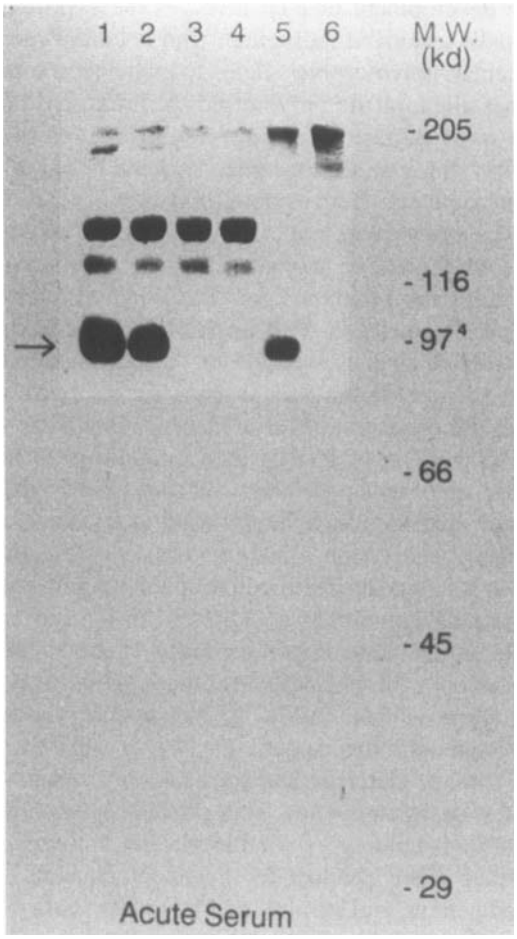

Fig. 2. Reactivity of acute-phase sera from patient G.H. with platelets from a variety of sources. Lane 1, platelets from a PL^{A2}/PL^{A2} donor; lane 2, platelets from a PL^{A1}/PL^{A2} donor; lanes 3 and 4, platelets from a PL^{A1}/PL^{A1} donor; lane 5, platelets from a patient with Glanzmann thrombasthenia; lane 6, molecular weight standards. Detergent-solubilized platelets were separated using 10% SDS-PAGE, transferred to nitrocellulose, and incubated serially with diluted patient sera and ^{125}I-labelled anti-human IgG. These sera recognized platelet proteins of ~135 kDa (anti Bak^a, expressed on GP IIb) and ~90 kDa (anti PL^{A2}, expressed on GP IIIa, absent in platelets from the PL^{A1}/PL^{A1} donor). The sera also contained antibodies reactive with an unidentified ~85-kDa protein present on platelets from a patient with Glanzmann's thrombasthenia (lane 5), which comigrated with GP IIIa in unidimensional SDS-PAGE (arrow). Lanes 1–4 were employed platelets from a Bak^a positive donor. The bands at ~120 kW represent a GPIIb fragment induced by solubilization. The bands at ~220 kD presumably represent platelet-associated IgG.

induced by transfusion of plasma containing anti-Br^a antibodies, has also been reported [9]). Genotyping, by reverse hybridization, revealed that the patient's platelets were PL^{A1}/PL^{A1}; Bak^a/Bak^b; Pen^a/Pen^a; and Br^b/Br^b. These results are consistent with her PTP resulting from an antibody with specificity for Br^a.

DISCUSSION

Posttranfusion purpura is characterized by acute onset of severe thrombocytopenia occurring approximately 5–14 days after transfusion [1–3]. Although packed red blood cells and whole blood [2,3] precipitate PTP most frequently, the development of this syndrome has also been associated with exposure to numerous other blood products, such as freeze-thawed red cells [10], leukocyte-poor red cells [11], and even fresh (but not frozen) plasma [12]. PTP was first described in 1961 by Shulman et al. [13], who identified a complement-fixing antibody, directed against a heterologous platelet antigen which he denoted PL^{A1}, in the sera of 2 individuals who developed thrombocytopenia following blood transfusion. The syndrome occurs primarily in multiparous women who have been sensitized to foreign platelet antigens during prior pregnancies. In the cases discussed above, for example, patient M.F. had four prior pregnancies, while patient G.H. had a prior ectopic pregnancy. Prior transfusions may also sensitize patients to foreign platelet antigens, and this mechanism may have contributed to the development of PTP in patient G.H.

As illustrated by both patients, the severe thrombocytopenia characteristic of PTP is often accompanied by bleeding [1–3]. Bleeding occurs at sites typically involved by "platelet-type" bleeding, such as the skin, mucous membranes, and gingiva. Intracranial hemorrhage may occur in some individuals, although the incidence of this often lethal complication varies among series [1–3,14]. Attempts to elevate the platelet count of affected individuals by platelet transfusion are usually futile, with such transfusions frequently accompanied by severe systemic responses resembling leukoagglutinin reactions, and with transfused platelets rapidly destroyed. Even platelets which lack the antigen implicated in the pathogenesis of specific cases of PTP are either only transiently effective [15], or ineffective [16], in inducing a significant increment in the platelet count of affected individuals.

The diagnosis of PTP is a clinical one, and should be suspected in an individual who develops thrombocytopenia within a 3–14-day period following transfusion of any blood product. Frequently, patients will display additional causes of thrombocytopenia as well, as illustrated by the possible presence of concomitant nafcillin-induced thrombocytopenia preceding the onset of PTP in patient M.F. In such cases, though the diagnosis of PTP is more difficult, it must not be overlooked, since it is likely that a significant obstacle to the appropriate diagnosis of PTP is the failure of clinicians to consider this disorder [14]. Indeed, underdiagnosis may contribute to the very low reported incidence of PTP. Furthermore, since prompt initiation of therapy appears to shorten the duration of thrombocytopenia, and therefore may reduce PTP-related morbidity and mortality [1,14], it is likely that main-

taining a high level of awareness of this disorder when evaluating thrombocytopenic individuals may improve patient outcome.

Serologic studies are also of use in the diagnosis of PTP. The demonstration of a high-titer, complement-fixing antibody which is reactive with a broad panel of platelets, including those from the donor (if available) is consistent with the diagnosis. The interpretation of such studies, however, may frequently be confused by the concurrent presence of anti-Human Leukocyte Antigen (HLA) antibodies [1,3,17–20]; such antibodies were present in the sera of both patients described in this report, making the *precise immunologic* characterization of their episodes of PTP difficult. A potentially useful study, which can be performed by the clinician when platelet serologic studies are not readily available, is a simple bedside test which can detect potent platelet-reactive antibodies capable of inducing platelet lysis or agglutination [21]. To perform this study, platelet-rich plasma is obtained by low-speed centrifugation of citrate-anticoagulated blood from a normal donor. This is mixed in a 1:1 ratio with platelet-poor plasma from the patient under evaluation. The mixture of these two samples will initially appear cloudy due to the presence of dispersed platelets from the normal platelet-rich plasma. However, clearing of this plasma mixture following a 30-min incubation at 37°C is consistent with the presence of a potent antiplatelet antibody which either induces platelet aggregation, or fixes complement, thereby leading to platelet lysis. Platelet-reactive antibodies of this nature are characteristic of PTP, although they may occur occasionally in patients with other types of immune-mediated thrombocytopenia, such as quinidine-induced purpura [21]. The sensitivity and specificity of this assay have not been rigorously determined, however, and therefore it should be employed only in the appropriate clinical setting, and interpreted with caution. False-negative results may be caused, for example, by a lack of specific antigens on the platelets of the normal donor used in the assay. Nevertheless, a positive assay suggests that an immune-mediated platelet-destructive process, consistent with PTP, may be present.

More specific platelet serologic methods [1,19], and more recently, molecular genotyping [22–24], have also been shown to be of utility in diagnosing PTP as well as in investigating its pathogenesis (see below). Platelets express a number of antigenic epitopes, which are attributable to polymorphisms in discrete regions of platelet cell-surface glycoproteins [25,26]. Several different systems of nomenclature, based on the chronological discovery of the platelet polymorphism [27,28], the individual in whom the polymorphism was first discovered, the platelet glycoprotein expressing the polymorphic epitope, or the molecular alteration responsible for the polymorphism, have been used to describe these alloantigen systems [25] (Table I). The initial pathophysiologic event responsible for the development of PTP involves the exposure of a previously-sensitized individual, who is homozygous for a particular polymorphic allele, to platelets expressing the other allele of the polymorphism. Prior sensitization occurs most frequently during pregnancy; sensitization to the PL^{A1} antigen, for example, has been found to occur in approximately 1 of every 1,000 pregnancies in the Caucasian population, and in approximately 6% of homozygous PL^{A2}-positive women [29]. These observations account for the relatively greater frequency of PTP in multiparous females [1–3]. Transfusion-induced exposure of such sensitized individuals to "foreign" platelets or platelet particles induces an anamnestic response, which leads to the clearance of these incompatible cells. However, the paradox of PTP is that, in addition to foreign platelets, autologous platelets are also destroyed [1–3]. Several hypotheses have been raised to account for this perplexing observation. One hypothesis suggests that autologous platelets are destroyed following binding of antigen-antibody complexes containing the foreign antigen [30]; however, little direct evidence exists in humans which supports this postulate. Another hypothesis is based on the premise that, following transfusion, platelets of the affected individual acquire the phenotype of the transfused, foreign platelets, and thus undergo alloantibody-mediated destruction [31]. This process presumably occurs through binding of soluble platelet antigens in the transfused blood product to the intact platelets of the affected patient, and is supported by in vitro data demonstrating that soluble PL^{A1} antigen is present in stored blood, and that incubation of PL^{A1}-negative platelets in stored plasma leads to their assumption of a PL^{A1}-positive phenotype [13,31]. However, this mechanism, though attractive, fails to explain the observation that thrombocytopenia has been reported to persist for more than 1 month in some individuals affected with PTP [20,32]. Another hypothesis suggests that exposure to foreign platelets induces the formation of an autoantibody reactive with autologous platelets [33,34]. This intriguing hypothesis has been advocated by Aster [35], and is supported by a limited number of reports which have demonstrated the development of antibodies, which recognized immobilized proteins distinct from both glycoprotein IIb or IIIa (on which the majority of platelet alloantigens are expressed), in patients with PTP. However, the identity of these potential autoantigens has not been determined; furthermore, the inability of Shulman et al. [13] to reinduce thrombocytopenia by infusion of a patient's own acute phase plasma into that individual following recovery from an episode of PTP argues against a pathophysiologic role for autoantibodies in the development of this disorder [13]. Thus, the paradox of PTP remains, and it is possible that the inability to identify a single, unifying mechanism to account for this disorder reflects a multifactorial pathogenesis.

TABLE I. Platelet Alloantigen Systems Implicated in the Development of PTP*

Serologic designation	Alternative designation	Phenotype frequency	Population studied	Antigen location	Genetic polymorphism-based nomenclature**
PL^{A1} (HPA-1a)*	Zw^a	.957–985	Caucasian	GPIIIa	GPIIIa
		.996	African-American		
		.999	Japanese		
PL^{A2} (HPA-1b)	Zw^b	.265–.270	Caucasian	GPIIIa	Pro_{33} GPIIIa
Bak^a (HPA-3a)	Lek^a	.860–.893	Caucasian	GPIIb	GPIIb
		.789	Japanese		
Bak^b (HPA-3b)	Lek^b	.508–.641	Caucasian	GPIIb	Ser_{843} GPIIb
		.707	Japanese		
Pen^a (HPA-4a)***	Yuk^b	.999	Caucasian		GPIIIa
		.999	Asian		
Pen^b (HPA-4b)	Yuk^a	0.0	Caucasian		Gln_{143} GPIIIa
		.017	Asian		
Br^b (HPA-5a)	Zav^b Hc^a	.992–.999	Caucasian	GPIa	GPIa
Br^a (HPA-5b)	Zav^a	.180–.206	Caucasian	GPIa	Lys_{505} GPIa

*HPA, human platelet antigen; GP, glycoprotein.

**As proposed by Newman et al. [25].

***Though the Pen^a alloantigen appears to have the same amino acid sequence as PL^{A1}, serological studies suggest that it posseses a specificity distinct from the latter.

Of the platelet alloantigen systems described to date, the PL^{A1}/PL^{A2} polymorphism has been shown to be the one most frequently involved in the pathogenesis of PTP (approximately 80% of cases) [1]. Platelets from approximately 98% of the Caucasian, 99.6% of the African-American, and 100% of the Asian population bear the PL^{A1}/PL^{A1} phenotype (Table I) [14]. Thus, most donor platelets are PL^{A1}-positive, and are potentially able to induce PTP in a PL^{A2}-homozygous recipient. Since approximately 1% of individuals are PL^{A1}-negative, it is uncertain why PTP does not occur more frequently, since in a single large hospital several hundred individuals per month may receive blood products. In contrast, some PL^{A1}-homozygous individuals may occasionally develop PTP in association with antibodies reactive with PL^{A2}. This was the case in patient G.H., who was found to be a PL^{A1} homozygote whose episode of PTP was associated with the development of such antibodies [4] (Fig. 2), in addition to antibodies with specificity for other platelet glycoproteins (see Case Reports).

As demonstrated by both patients described in this report, other platelet antigen systems in addition to the $PL^{A1/A2}$ system have been implicated in the pathogenesis of PTP, although each of these is probably involved in <5% of all PTP cases (Table I). These include the Bak^a/Bak^b (HPA-3a/3b) [1,4,7], Br^a/Br^b (HPA-5b/5a) [1,8], and Pen^a/Pen^b (HPA 4a/4b) [14] systems. Sera from patient G.H., for example, contained anti-Bak^a antibodies, while patient M.F. is approximately the third individual reported who has developed PTP in association with antibodies against Br^a [1,8,9]. The frequency of the Br^a allele in the European and U.S. populations is reported to be only 20–23%, with approximately 99% of German individuals homozygous for Br^b, the high-frequency antigen of this allotypic system [14,36]. The distribution of these alleles in Hispanic individuals, such as patient M.F., has not been reported, though Br^a occurs only in approximately 5% of South American Indians [14].

Although confirmation of the diagnosis of PTP requires serologic studies, the increasing application of molecular techniques to diagnostic clinical pathology may play an increasingly important role in the characterization of this disorder in the future. Though not able to assess antibody specificity, these techniques allow identification of the patient's platelet genotype, and thus provide information useful in determining the relevance of potentially-pathogenetic antibodies identified in specific cases of PTP. Several techniques for platelet genotyping have been developed, including allele-specific oligonucleotide hybridization (ASO) [23], determination of restriction fragment-length polymorphisms of PCR-amplified DNA [37], and allele-specific PCR [22]. These methods are rapid, and in most cases yield easily-interpretable results. Such studies greatly facilitated the immunologic characterization of the episode of PTP experienced by patient M.F. (see Case Reports).

Though PTP is a self-limited disorder, specific therapy does appear to diminish the duration of thrombocytopenia. This conclusion is derived primarily by comparing the outcomes of therapy in patients with PTP who were treated within the last 10 years with those of *historical* controls, since the rarity and heterogeneity of this disorder precludes the conduction of randomized, controlled therapeutic trials. Prior to the use of plasmapheresis or intravenous immunoglobulin for treatment of PTP, the duration of PTP-induced thrombocytopenia ranged from approxi-

mately 10 days to 3 weeks or more [20]. In contrast, more recent series consisting of treated patients suggest that PTP-induced thrombocytopenia generally begins to resolve within 2–4 days after the initiation of effective therapy (Fig. 1) [1]. Several modalities are currently available for therapy of PTP. High doses of corticosteroids have induced dramatic responses in a few individuals [38–40], even, on occasion, those refractory to other modes of therapy [41]. In general, however, corticosteroids have not been demonstrated to possess consistent efficacy in the therapy of PTP [1–3]. A more effective intervention for patients with PTP, efficacious in approximately 80% of patients, is plasmapheresis [17,42]. However, the utility of plasmapheresis is limited by the requirement of obtaining venous access with large-bore catheters in patients who are severely thrombocytopenic. Primarily for this reason, as well as numerous recent reports suggesting efficacy which is at least equal to that of plasmapheresis, intravenous immunoglobulin has become an increasingly popular therapy for PTP [1–3,43–45]. Intravenous immunoglobulin is delivered at doses similar to those used in the therapy of other immunohematologic disorders, such as autoimmune thrombocytopenia purpura (e.g., 1 g/kg/day for 2 consecutive days, or 0.4 g/kg/day for 5 consecutive days, for a total dose of 2 g/kg); it is possible that smaller doses than these might also be effective, though this has not been investigated.

Finally, the importance of routine supportive care in the treatment of patients with PTP cannot be overemphasized. Since the transfusion of platelet concentrates is generally without efficacy in this disorder, and may induce severe systemic reactions as well as additional HLA allosensitization, these should be reserved for life-threatening hemorrhage. Likewise, since packed red-cell preparations may be contaminated with platelets or platelet fragments, these are also best avoided. If therapy for severe bleeding-related anemia is required, it is recommended that washed red cells be administered, although it should be remembered that platelet- and leukocyte-depleted red-cell preparations have been implicated in the induction of PTP [10,11], and may also be capable of inducing allosensitization. Invasive procedures such as arterial punctures or insertion of central venous catheters should be avoided unless absolutely necessary, and patients should not be allowed to ambulate without assistance until the platelet count has returned to a safe range.

By maintaining a high clinical suspicion for cases of PTP, and initiating appropriate therapy promptly after a clinical diagnosis is made, it is likely that the morbidity and mortality associated with this disorder may be further diminished. Though achievement of this goal alone represents a worthwhile focus for clinical hematologists, the enigma of how and why this disorder occurs remains. It is likely that this puzzle, as well, will eventually be solved, and perhaps shed additional insight into the pathogenesis of other immune hematologic disorders as well.

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